



EQUINE ROUNDS

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OAAM IN HORSES

By Andy Looney '89

Malformations of the vertebral column are among the most severe congenital defects seen in domestic animals. The severity is due to the fact that the fetal vertebral canal, the cylinder formed by the vertebrae which houses the spinal cord, is often severely compromised by the deformity and consequently, spinal cord compression results in severe neurologic signs. The signs of occipitoatlantoaxial malformation (OAAM), a serious malformation of the equine vertebral column, may be seen either at birth or shortly thereafter in affected foals. Although this disease has been seen sporadically in many breeds of horses, it is recognized as an inherited disease in Arabian horses.

Vertebrae are derived embryonically from paired segments or blocks of tissue known as somites. In the developing embryo, these somites align in rows on both sides of a tube of nervous tissue destined to become the spinal cord. The first four or five somites are called the occipital somites because parts of them fuse to form the occipital cartilages of the skull. Parts of the remaining somites form all of the vertebrae. The cervical (or neck) vertebrae are the first vertebrae to develop from the somites after the skull cartilages have been formed.

The rather long name, occipitoatlantoaxial malformation, is derived from the three skeletal structures which are abnormally fused and malformed in the affected foals during their embryonic development. These three structures are the occipital cartilages of the hind part of the skull, and the atlas and the axis, the first and second vertebrae,

respectively, of the vertebral column. If the blocks of embryonic tissue, the somites, which are destined to form these structures fail to segment properly as the embryo develops and as the spinal cord grows, vertebral malformation results and distortion of the nervous tissue in the cord occurs. OAAM is due to a failure of the occipital somites to segment, or they form their respective blocks of tissue from the somites which form the atlas, the first vertebra of the neck. Hence, the occipital bones of the skull and the atlas become fused in the fetus. As a result, the somites responsible for forming the second vertebra in the neck, the axis, lose their proper patterning, and the axis also becomes grossly malformed.

In most foals with OAAM, there is no discernible atlanto-occipital (skull-spine) joint, the normally moveable articulation between the head and the neck, and this is replaced with a nonfunctioning symmetric bony fusion. Besides the obvious reduction in mobility, the fusion also results in a narrowing of the vertebral canal and less space for the spinal cord. The atlas, once fused to the occipital bones, loses its normal anatomical features. In place of the normally flattened, wide processes ("wings"), attenuated knobby projections can be found. These appear as small bumps and can be seen and palpated in affected foals on both sides of the upper neck. The atlas in foals with OAAM also has a tendency to develop as if it were the occipital bone, assuming the appearance of the hind part of the skull instead of a vertebra.

In normal foals, the axis, or second vertebra, has a pointed process in front, known as the dens, which functions with the atlas to provide rotation for the head on the neck. In foals with OAAM, the axis has a



malformed dens, usually smaller than that found in normal foals. Consequently, this vertebra is misaligned in the spinal column, slipping below the joint it forms with the atlas and causing displacement and damage to the spinal cord. The axis of affected foals also has a tendency to assume the appearance of the atlas. The normally very slender side processes of the axis become broad like the wings of the atlas, probably in an attempt to compensate for the abnormal atlas fused to occipital bones of the skull.

Most of the clinical signs seen in foals with OAAM can be attributed to spinal cord compression and displacement resulting from the vertebral deformity. These signs may be present at birth or develop within the first few weeks or months of life. If the deformity is severe enough, neurologic signs will be present at birth. The foal may fail to rise to nurse due to its inability to stand. Or if able to stand, it may exhibit extreme incoordination or weakness. Positioning the neck in order to nurse causes further difficulty and falling down is a common result of the severe incoordination. An important diagnostic feature of the disease is the posture of the neck resulting from the lack of mobility. Due to inability to flex the fused joint, the neck appears extended and stiff and the nose is often held slightly higher than normally.

A palpable "bump" or knob may be visible on each side of the upper neck where the "wings" of the atlas are usually felt. Occasionally, a "clicking" sound may be heard as the foal moves its neck. The "click" has been attributed to the attenuated dens of the axis temporarily snapping from its displaced position to its normal position in the atlas. Most of the spinal cord compression found in newborn foals occurs when this improper movement of the axis against the fused atlas causes severe pinching, concussion and compression of the cord and results in incoordination and paralysis.

In some affected foals, neurologic signs resulting from spinal cord compression may not

appear until several weeks or even months after birth. These foals are born with the same malformations as the neonatal OAAM foals; but at birth, there is less encroachment upon the space occupied by the spinal cord in the vertebral canal. Problems occur as the foal begins to grow. The existing space for the cord fails to enlarge simultaneously with the growing nervous tissue. With daily movement, unequal pressures on the cartilages of the atlas and axis lead to further (acquired) distortion of the joint surfaces. Surrounding soft tissues thicken the joint capsules in an attempt to provide more support to the malformed joints, yet this further limits movement in the upper neck. There is a gradual encroachment upon the canal and a progressive spinal cord compression which advances rapidly once signs appear. The most remarkable sign is the gait which may at first appear as an unsteadiness that rapidly progresses to a spasticity and incoordination seen in all four legs, but is most marked in the forelimbs. An extended neck posture also may be noted in these foals, as well as the bony prominences on each side of the upper neck.

Diagnosis of occipitoatlantoaxial malformation is usually confirmed radiologically. X-rays of the skull-neck junction clarify the anatomic deformities which precipitate the neurologic signs in the affected foals. Unfortunately, surgery cannot be recommended due to difficulty in repairing malformed bony tissue and the already severely injured and compromised spinal cord. Most foals are humanely euthanized shortly after the onset of clinical signs.

OAAM as a disease *per se* is seen only in the Arabian horse and there is sufficient evidence to support autosomal recessive inheritance in this breed. While further breeding trials with affected and/or carrier horses and subsequent studies of development are needed to confirm this pattern of inheritance, breeding to sires known to produce progeny with OAAM should be discouraged.



OVERO CROSSES LETHAL WHITE FOALS AGANGLIONOSIS

Thanks to Drs. Noden and Forsythe

By Koen Loeven '90

Abstract

White foals born from overo parents die from colic during the first few days of life. The problem also is known as the White Foal Syndrome but should not be confused with the gene for dominant lethal white color. The overo condition involves abnormal development of the nervous system associated with the large and small intestine.

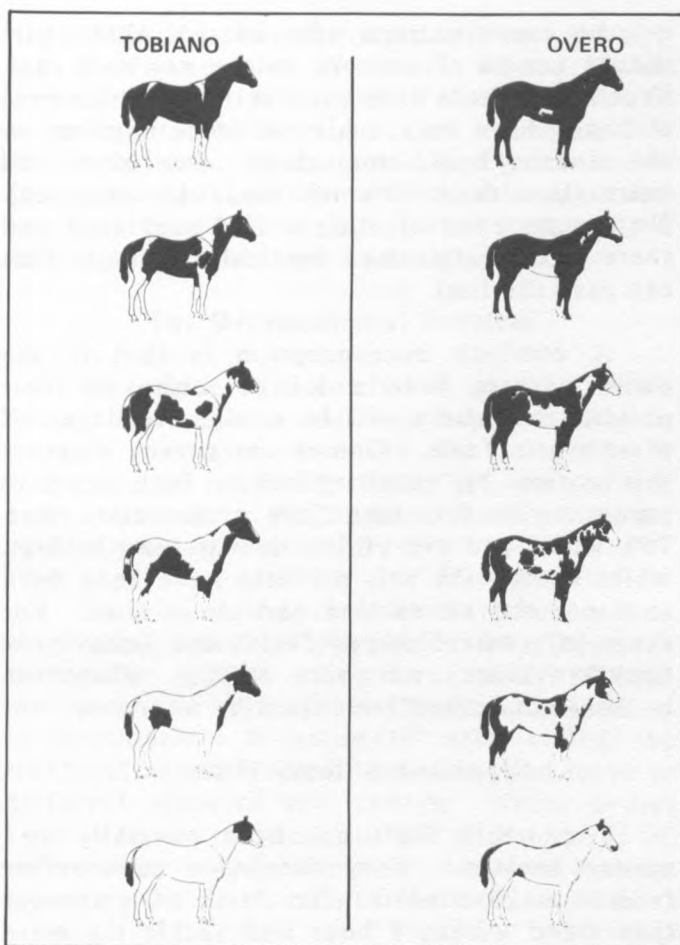
Introduction to Color Patterns

OVERO is a color pattern recognized by both the American Paint Horse Association and the Pinto Association of America, Inc. The other major pattern recognized by these organizations is the TOBIANO.

The OVERO is a white spotting pattern where the white patches tend to be located on the horse's sides. The top of the animal's back is usually colored and the white patches do not usually cross over the back from one side to the other. The outlines of the spotting pattern are often jagged.

The TOBIANO pattern, in contrast, tends to have white over the top of the back with patches spreading down the sides. This pattern usually has the dark color located on the horse's sides and there is less white on the face as a rule. The outlines of this spotting pattern tend to be smooth. The legs are generally white.

The genetic mode of inheritance of these patterns has not been well established in the literature. However, we are reasonably sure that the tobiano pattern is a dominant trait.



Reports have suggested that the overo pattern is basically a recessive trait but hard facts are lacking to support this idea.

As you can see from the above illustrations there is an almost infinite gradation of white and colored areas for both of these spotting patterns.

The White Foal Problem

When breeders cross an overo mare with an overo stallion, completely white foals are sometimes born. Regardless of the sex of the foal, all die with signs of colic within 1 to 6 days. Most of these foals appear healthy at birth, stand and suckle the mare. They show signs of colic within 5-24 hours (avg.=13 hrs) and usually are dead by 46 hours after birth.



An overo pattern with considerable white should not be of concern in the newborn foal. True white foals have pink skin, pale blue eyes and may have only a hint of some pigment on the muzzle, hoof, stomach or some black tail hairs (less than 10% of the foals reported). No reports exist of such a foal surviving and there is no surgical or medical treatment that can save the foal.

A common misconception is that if the overo parents have a lot of white in their pattern that there will be a high incidence of these white foals. One recent survey disputes this notion by reporting white foals born to parents with less than 25% white, more than 75% white and everything in between. In fact, white foals with this problem have been born to non-overo mares that had overo sires. For example, one of these foals was born to a buckskin mare and overo stallion where the buckskin mare had been sired by an overo.

Signs and Autopsy Findings

The white foals are born normally and appear healthy. They develop a suck reflex from 1 to 20 minutes after birth. On average they stand within 1 hour and suckle the mare within 2 hours. However, they never pass meconium.

Meconium is the "manure" of a newborn infant that accumulates in the gut while the foal is in the womb. Meconium is normally passed by the foal during the first 24 hours after birth and appears as mucous covered, hard or paste-like pellets that are black or dark brown in color.

The foals begin to show signs of colic within 5-24 hours (avg. = 13 hours). These signs include straining to defecate, looking at their sides, unwillingness to get up, rolling, mild to violent thrashing, elevated respiration and heart rates and sweating or elevated body temperatures.

On closer examination these foals have reduced but usually completely absent gut

sounds and no feces in their rectums. These animals do not respond to enemas, which are often given to foals in order to help pass meconium. If there is time to do blood studies, the veterinarian finds normal values with the possible exception of some increase in white blood cells in response to stress.

Since all of these foals die within the first week after birth, usually within 2 days, the rest of the picture is presented during the autopsy. The rectum and entire small colon are found to be pale, very small/narrow and tightly contracted. The small intestine is often distended and dilated with ingested milk while the cecum and large colon are distended with large amounts of impacted meconium. Other reports have indicated that varying portions of the large colon may appear constricted like the small colon and contain no meconium.

The Cause - Aganglionosis

Colic in the overo white foal syndrome is due to the impaction of meconium and ingested milk which leads to distention and severe pain. The meconium and milk are impacted because peristalsis fails to occur in the portions of the gut behind the impaction site. Peristalsis is the normal muscular activity in the wall of the gut that is responsible for moving food and feces backward. This muscular activity is much like a wave of contractions that passes along the length of the gut tube. Peristalsis is a highly coordinated event and is analogous to grasping a flexible piece of water-filled tubing with your fingers and stripping the water out as you hold one end and run your fingers down the length of the tube.

Peristalsis, like any other muscular activity, requires nerves to trigger the contractions. However, the gut is unusual in that we can think of it as having its own, almost independent nervous system. In fact, the wall of the gut has about the same number of nerve cells as the entire spinal cord. Although there are "external" nerve fibers that connect with the gut and regulate its activity,



most of the nerve cells are located inside the muscular wall of the gut tube in little groupings called myenteric and submucosal plexuses or ganglia.

AGANGLIONOSIS literally means "without ganglia". When pathologists use the microscope to examine the gut wall of these white foals, they fail to find these critical nerve ganglia in the small colon and all or parts of the large colon and even portions of the small intestine. Peristalsis that normally moves things through the GI tract cannot occur when there are no plexuses.

In February of 1987 the New York State College of Veterinary Medicine's Pathology Department analyzed one of these white foals. Their report indicated an absence of myenteric and submucosal ganglia in the rectum, small colon, large colon and most of the small intestine. Another interesting finding in these cases is that the motor nerves going to, or the sensory nerves coming from these areas of the gut are intact and functional.

An additional finding was a small, contracted small colon. One might very well ask why and how the small colon can get so tightly contracted when the nerve ganglia are absent. There is a difference between well-coordinated peristaltic contraction and contraction of a segment of the bowel that is independent of neighboring contractions. The muscle in the gut wall is smooth muscle and is not under conscious or voluntary control like the muscles of arms or legs. Smooth muscle is an "excitable" type of muscle which contracts on its own or if stimulated by irritation or stretching. One function of the myenteric ganglia is to control this tendency to contract (i.e., to inhibit contraction when appropriate). In the absence of this control, the smooth muscles (with minds of their own, so to speak) contract and stay contracted.

Early reports seemed to indicate that the colic was associated with a congenital stenosis of the colon or a condition called rectal atresia. Congenital stenosis is just a fancy

way of saying that the colon did not develop with a large enough diameter. Rectal atresia is a condition where the rectum fails to connect with the anus or open to the outside of the animal. These conditions generally do not appear in association with this syndrome but have been mistaken for what is actually a very tightly constricted small colon.

The Developmental Problem

Why does this condition occur? When during development does this happen? Why is there a correlation between the color of the foal and this problem? These are some of the many questions which have been and are currently being researched.

Initially it was thought that the problem involved a defect in the precursor cells which eventually become the nerve cells of the myenteric and submucosal plexuses. Very early in development a group of cells called the **NEURAL CREST CELLS** multiply and move to different areas of the embryo. These neural crest cells are critical in the development of the central and peripheral nervous systems including the nerve cells of the gut ganglia.

The neural crest cells also develop into cells that eventually produce the pigments which are responsible for coat color. These cells are called **MELANOCYTES**. Since the overo white foals do not have skin or hair color (remember that white is really the absence of coloration) and also lack myenteric and submucosal ganglia, many researchers felt that the problem originates with a malfunction of the neural crest cells. The hypothesis was that perhaps they fail to divide properly or fail to move to their proper location or fail to become the cells that they are supposed to become.

Very recent studies indicate that this does not seem to be the case. Within the last three years we have learned that the problem stems from an inherent flaw in the gut wall itself rather than from a neural crest or nerve cell development defect. In carefully



controlled studies researchers have shown that when the precursor cells of the myenteric/submucosal nerve ganglia migrate to and reach the gut wall, something in the gut wall itself prevents them from entering the gut wall and assuming their proper positions for further development. It makes sense that the aganglionosis of overo white foals is not a defect of the neural crest cells since other parts of the nervous system of the foal (which also originate from this group of cells) seem to develop properly.

Conclusion and Recommendations

There is much which we still do not know concerning this syndrome. One of the largest gaps in our knowledge concerns the genetic basis and mode of inheritance of this condition. The syndrome of aganglionosis is not limited to the horse. Similar conditions have been found in conjunction with certain color patterns in mice. In humans aganglionosis comes in varying degrees of severity and is called HIRSCHSPRUNG DISEASE. The most severe condition of this disease is called the ZUELZER-WILSON SYNDROME which is very similar to the overo white foal syndrome and involves aganglionosis throughout the entire large intestine.

In both mice and humans aganglionosis is inherited as a recessive trait. This mode of inheritance has not yet been established for the Overo White Foal Syndrome. The research that is needed to determine the mode of inheritance will require careful analysis of breeding records and controlled test matings. Cooperation between the veterinary community, breeders and the two registries, the American Paint Horse Association and the Pinto Association of America, Inc. will be needed. Breeding recommendations then can be established which would help eradicate this deadly syndrome.

Our thanks to the American Paint Horse Assoc.
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INFERTILITY AND ANEUPLOIDY IN HORSES

By Linda A. Isaman '89

Within the cell, the material containing the genetic information is in distinct paired units called chromosomes. When the cells divide the chromosomes duplicate, and following division each of the two new cells has one complete set of paired chromosomes. Horses' cells have 64 such chromosomes per cell, two of which are sex chromosomes. The paired sex chromosomes are designated as "X" or "Y". If a cell is XY then it is a cell of a stallion, while an XX cell is that of a mare. Thus the X and the Y chromosomes hold the power to determine sex. In the completely normal case, a stallion will be 62XY (62 refers to the number of non-sex chromosomes, or autosomes) and a mare will be 62XX.

In the human population, abnormalities in chromosome numbers due to errors during cell division can cause fertility problems. In addition, women or men with abnormal numbers of sex chromosomes (referred to as sex chromosome aneuploidy) can have nearly normal outward appearances but reproductive malfunctions. Aneuploidy may be an extra chromosome, for example, XXX or XXY or lack of a chromosome, designated XO or YO. To further complicate matters, individuals may have a mixture of normal (XY or XX) and abnormal (e.g., XXX, XXY) cells; a condition called mosaicism.

Knowledge of such abnormalities in the human population prompted scientists interested in equine fertility to examine mares with chronic infertility to see if some of these mares had abnormalities in their sex chromosomes. Although resulting studies have yielded some answers, more research is still needed.

The Mare

The outward appearance or phenotype of mares with sex chromosome aneuploidy is usually normal, although the mares may be somewhat smaller in size overall. Such mares



may respond to teasing by a stallion with receptivity, mild interest, or violent aggression, but usually with no response. If the mare does display estrous behavior, she usually does not follow a cyclical pattern; rather she may show signs of estrus for a few days and then become completely disinterested in the stallion for prolonged periods of time. Other behavior may appear normal.

Of course, knowing that many otherwise normal mares found to have sex chromosome aneuploidy never show normal estrous behavior, it is tempting to blame all erratic estrous behavior or poor fertility on abnormalities of the sex chromosomes. However, there are many other recognized causes of anestrus or erratic estrus, ranging from season of the year to poor nutrition or management. Sex chromosome aneuploidy should not be blamed for most fertility problems.

A veterinarian may suspect the lack of an X chromosome in a mare once other more common causes of poor reproductive efficiency have been ruled out. At this point, the veterinarian will look for small ovaries with reduced activity, a small uterus, and a toneless cervix. Unfortunately the mare, unlike females in other species with sex chromosome abnormalities, does not show an enlarged clitoris or any other distinctive outward signs. Rather, a veterinarian must rely on internal signs, such as small ovaries lacking primordial germ cells (the cells giving rise to ova) and reduced branching of glands in the lining of the uterus, one indication of low levels of estrogens in the blood due to lack of follicles on the ovary.

Mares whose cells contain a mixture of chromosome numbers may show chromosome number differences within the same tissue, or between tissues. The distribution of cells with abnormal chromosomes, of course, will determine how the mare will look and behave, as well as how she will function. Approximately one-third of mares that are infertile due to chromosome abnormalities are mosaics.

Most reported cases of sex chromosome aneuploidy are presented to veterinarians because of a lack of proper reproductive function, such as failure to cycle, failure to conceive, or failure to carry foals to term. Women with sex chromosome aneuploidy are known to have a much higher abortion rate if they are not completely sterile. All mares lacking an X chromosome (XO) have been found to be sterile. Less commonly reported are mares with an extra X chromosome (XXX); these mares also have improper sexual functions.

Such cases are obvious enough once identified. What increasingly concerns researchers, veterinarians, and those managing breeding farms, however, is the possibility of a large number of unidentified mares with sex chromosome aneuploidy that are not sterile but have reduced reproductive efficiency. These mares, perhaps cycling irregularly or suffering early embryo loss, represent a potentially large economic burden as they may be treated for other causes of infertility to no avail.

The Stallion

Mosaicism is the most common sex chromosome aneuploidy in stallions. Mosaics are reported to show male pseudohermaphroditism, that is, they possess some organs and characteristics of both sexes (a true hermaphrodite would have a complete set of sex organs of both sexes). These stallions generally have an overall phenotype of a mare, but also have some organs associated with the male sex such as a small penis in an abnormal location. Testicles remain in the abdomen of such stallions, never descending into the scrotum as is normal. Although these stallions may mount and ejaculate some fluids, sperm are absent. The problem is not judged to be as serious in the male as in the female, because a sex chromosome abnormality can be diagnosed simply by looking at the horse.

Sexual differentiation leading to a fertile adult requires gonads (ovaries or testes) of normal function to be present. Sex



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chromosomes must be normal both in morphology and number for normal gonads to develop. An abnormal number of sex chromosomes hinders or prevents formation or functioning of gonads, effectively reducing or even destroying fertility. As studies of infertility in the horse continue, more cases of sex chromosome aneuploidy may be recognized. If sex chromosome aneuploidy causes abnormal sexual behavior, failed gonad development, increased rate of early embryonic loss and inefficient reproduction in the horse, as is known to happen in humans, then such chromosome abnormalities may represent a source of economic loss to horse breeders. Should this economic loss be great enough, examination of chromosomes through the process of karyotyping may become part of the evaluation for breeding soundness of horses with chronic infertility problems where no other causes are known.

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